

FORM PTO 1390
(REV 5-93)

US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY DOCKET NO.
2000_0486ATRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 USC 371U.S. APPLICATION NO.
(if known, see 37 CFR 1.5)
NEW 09/529715International Application No.
PCT/JP98/04658International Filing Date
October 15, 1998Priority Date Claimed
October 20, 1997

Title of Invention

FAST-DISSOLVING PHARMACEUTICAL COMPOSITION

Applicant(s) For DO/EO/US

Mamoru OHASHI, Kazuyoshi OGASAWARA, Yoshimi SHIRAI, Hiroshi FUJIOKA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 USC 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 USC 371.
3. ☐ This is an express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 USC 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 USC 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 USC 371(c)(2)). **ATTACHMENT A**
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 USC 371(c)(3)).
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 USC 371(c)(3)).
9. ☒ An executed oath or declaration of the inventor(s) (35 USC 371(c)(4)). **ATTACHMENT B**
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 USC 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98. **ATTACHMENT C**
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
ATTACHMENT D
13. ☒ A **FIRST** preliminary amendment. **ATTACHMENT E**
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

THIS DOCUMENT IS AUTHORIZED
TO BE REPRODUCED IN THE
FEDERAL REGISTER TO DEPOSIT
ACCOUNT NO. 93-0975-

420 Rec'd PCT/PTO 19 APR 2000

U.S. APPLICATION NO. (37 CFR 1.5) NEW 09/529715		INTERNATIONAL APPLICATION NO. PCT/JP98/04658		ATTORNEY DOCKET NO. 2000 0486A	
17. [X] The following fees are submitted BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): [X] Search Report has been prepared by the EPO or JPO \$840.00 [] International preliminary examination fee paid to USPTO (37 CFR 1.482) \$670.00 [] No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) \$690.00 [] Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$970.00 [] International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-33(4) \$ 96.00 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS	PTO USE ONLY
Surcharge of \$130.00 for furnishing the oath or declaration later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	62 - 20 =	42	X \$18.00	\$756.00	
Independent Claims	- 3 =		X \$78.00	\$	
Multiple dependent claim(s) (if applicable)			+ \$260.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$1,596.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28)				\$	
SUBTOTAL =				\$1,596.00	
Processing fee of \$130.00 for furnishing the English translation later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+	\$
TOTAL NATIONAL FEE =				\$1,596.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (\$40 per property).				+	\$40.00
TOTAL FEES ENCLOSED =				\$1,636.00	
				Amount to be refunded:	\$
				charged:	\$

09/529715

423 Rec'd PCT/PTO 19 APR 2000

- a. ☒ A check in the amount of \$1,636.00 to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. 23-0975 in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0975. A duplicate copy of this sheet is enclosed.

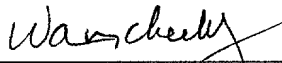
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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By



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April 19, 2000
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2000-0486A

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422 Rec'd PCT/PTO 19 APR 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :
Mamoru OHASHI et al. : Attn: BOX PCT
Serial No. NEW : Docket No. 2000-0486A
Filed April 19, 2000 :

FAST-DISSOLVING PHARMACEUTICAL COMPOSITION
[Corresponding to PCT/JP98/04658
Filed October 15, 1998]

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Prior to calculating the filing fee, please amend the above-identified application as follows:

IN THE CLAIMS

Please replace pages 18-20 of the English translation of the original PCT application, submitted herewith as Attachment A, with the attached sheets of pages 1-12.

REMARKS

Claims 1-12 of the original PCT application are replaced with replacement claims 1-62 which claims are presented to more particularly point out and distinctly claim the invention under U.S. practice.

Favorable action on the merits is solicited.

Respectfully submitted,

Mamoru OHASHI et al.

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April 19, 2000

PRELIMINARY AMENDMENT OF CLAIMS

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CLAIMS

1. A fast-dissolving pharmaceutical composition comprising micronized (R)-2-(4-bromo-2-fluorobenzyl)-
5 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-4-spiro-3'-pyrrolidine-1,2',3,5'-tetrone (hereinafter, referred to as "AS-3201").

2. The fast-dissolving pharmaceutical composition according to claim 1, wherein the mean particle size of the
10 micronized AS-3201 is less than about 10 μm .

3. The fast-dissolving pharmaceutical composition according to claim 1, wherein the mean particle size of the micronized AS-3201 is less than about 5 μm .

4. The fast-dissolving pharmaceutical composition
15 according to claim 1, wherein the mean particle size of the micronized AS-3201 is in the range of about 0.5 μm - about 3 μm .

5. A fast-dissolving pharmaceutical composition, which comprises micronized AS-3201 in a ratio of about 0.5 %
20 by weight - 5 % by weight, a diluent in a ratio of about 51 % by weight - about 93.8 % by weight, a disintegrator in a ratio of about 5 % by weight - about 35 % by weight, a binder in a ratio of about 0.5 % by weight - about 5 % by weight, and a lubricant in a ratio of about 0.2 % by weight - about 4 %
25 by weight, to the total weight of the pharmaceutical

composition.

6. The fast-dissolving pharmaceutical composition according to claim 5, wherein the mean particle size of the micronized AS-3201 is less than about 10 μm .

5 7. The fast-dissolving pharmaceutical composition according to claim 5, wherein the mean particle size of the micronized AS-3201 is less than about 5 μm .

8. The fast-dissolving pharmaceutical composition according to claim 5, wherein the mean particle size of the
10 micronized AS-3201 is in the range of about 0.5 μm - about 3 μm .

9. The fast-dissolving pharmaceutical composition according to claim 5, which comprises a diluent in a ratio of about 59 % by weight - about 88 % by weight, a disintegrator
15 in a ratio of about 10 % by weight - about 30 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight - about 3 % by weight.

10. The fast-dissolving pharmaceutical composition
20 according to claim 6, which comprises a diluent in a ratio of about 59 % by weight - about 88 % by weight, a disintegrator in a ratio of about 10 % by weight - about 30 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight
25 - about 3 % by weight.

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11. The fast-dissolving pharmaceutical composition according to claim 7, which comprises a diluent in a ratio of about 59 % by weight - about 88 % by weight, a disintegrator in a ratio of about 10 % by weight - about 30 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight - about 3 % by weight.

12. The fast-dissolving pharmaceutical composition according to claim 8, which comprises a diluent in a ratio of about 59 % by weight - about 88 % by weight, a disintegrator in a ratio of about 10 % by weight - about 30 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight - about 3 % by weight.

13. A fast-dissolving pharmaceutical composition, which comprises micronized AS-3201 in a ratio of more than 5 % by weight and less than about 25% by weight, a diluent in a ratio of about 16 % by weight - about 84.3 % by weight, a disintegrator in a ratio of about 10 % by weight - about 50 % by weight, a binder in a ratio of about 0.5 % by weight - about 5 % by weight, and a lubricant in a ratio of about 0.2 % by weight - about 4 % by weight, to the total weight of the pharmaceutical composition.

14. The fast-dissolving pharmaceutical composition according to claim 13, wherein the mean particle size of the

micronized AS-3201 is less than about 10 μm .

15. The fast-dissolving pharmaceutical composition according to claim 13, wherein the mean particle size of the micronized AS-3201 is less than about 5 μm .

5 16. The fast-dissolving pharmaceutical composition according to claim 13, wherein the mean particle size of the micronized AS-3201 is in the range of about 0.5 μm - about 3 μm .

10 17. The fast-dissolving pharmaceutical composition according to claim 13, which comprises a diluent in a ratio of about 29 % by weight - about 73.5 % by weight, a disintegrator in a ratio of about 20 % by weight - about 40 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight - about 3 % by weight.

15 18. The fast-dissolving pharmaceutical composition according to claim 14, which comprises a diluent in a ratio of about 29 % by weight - about 73.5 % by weight, a disintegrator in a ratio of about 20 % by weight - about 40 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight - about 3 % by weight.

20 19. The fast-dissolving pharmaceutical composition according to claim 15, which comprises a diluent in a ratio of about 29 % by weight - about 73.5 % by weight, a

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disintegrator in a ratio of about 20 % by weight - about 40 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight - about 3 % by weight.

5 20. The fast-dissolving pharmaceutical composition according to claim 16, which comprises a diluent in a ratio of about 29 % by weight - about 73.5 % by weight, a disintegrator in a ratio of about 20 % by weight - about 40 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight - about 3 % by weight.

10 21. The fast-dissolving pharmaceutical composition according to claim 1, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

15 22. The fast-dissolving pharmaceutical composition according to claim 2, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

20 23. The fast-dissolving pharmaceutical composition according to claim 3, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

25 24. The fast-dissolving pharmaceutical composition according to claim 4, which has a dissolution percentage of

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the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

25. The fast-dissolving pharmaceutical composition according to claim 5, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

26. The fast-dissolving pharmaceutical composition according to claim 6, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

27. The fast-dissolving pharmaceutical composition according to claim 7, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

28. The fast-dissolving pharmaceutical composition according to claim 8, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

29. The fast-dissolving pharmaceutical composition according to claim 9, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

30. The fast-dissolving pharmaceutical composition according to claim 10, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after

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the start of the dissolution test.

31. The fast-dissolving pharmaceutical composition according to claim 11, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

32. The fast-dissolving pharmaceutical composition according to claim 12, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

33. The fast-dissolving pharmaceutical composition according to claim 13, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

34. The fast-dissolving pharmaceutical composition according to claim 14, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

35. The fast-dissolving pharmaceutical composition according to claim 15, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

36. The fast-dissolving pharmaceutical composition according to claim 16, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

37. The fast-dissolving pharmaceutical composition according to claim 17, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

5 38. The fast-dissolving pharmaceutical composition according to claim 18, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

10 39. The fast-dissolving pharmaceutical composition according to claim 19, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

15 40. The fast-dissolving pharmaceutical composition according to claim 20, which has a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test.

20 41. The fast-dissolving pharmaceutical composition according to claim 21, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

42. The fast-dissolving pharmaceutical composition according to claim 22, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

25 43. The fast-dissolving pharmaceutical composition

according to claim 23, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

5 44. The fast-dissolving pharmaceutical composition according to claim 24, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

10 45. The fast-dissolving pharmaceutical composition according to claim 25, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

15 46. The fast-dissolving pharmaceutical composition according to claim 26, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

47. The fast-dissolving pharmaceutical composition according to claim 27, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

20 48. The fast-dissolving pharmaceutical composition according to claim 28, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

25 49. The fast-dissolving pharmaceutical composition according to claim 29, which has a dissolution percentage

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of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

50. The fast-dissolving pharmaceutical composition according to claim 30, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

51. The fast-dissolving pharmaceutical composition according to claim 31, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

52. The fast-dissolving pharmaceutical composition according to claim 32, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

53. The fast-dissolving pharmaceutical composition according to claim 33, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

54. The fast-dissolving pharmaceutical composition according to claim 34, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

55. The fast-dissolving pharmaceutical composition according to claim 35, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after

the start of the dissolution test.

56. The fast-dissolving pharmaceutical composition according to claim 36, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

57. The fast-dissolving pharmaceutical composition according to claim 37, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

58. The fast-dissolving pharmaceutical composition according to claim 38, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

59. The fast-dissolving pharmaceutical composition according to claim 39, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

60. The fast-dissolving pharmaceutical composition according to claim 40, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

61. The fast-dissolving pharmaceutical composition according to claim 1, which contains as a stabilizer at least one acidic substance having an acidity more potent than that of AS-3201.

[illegible]

DESCRIPTION

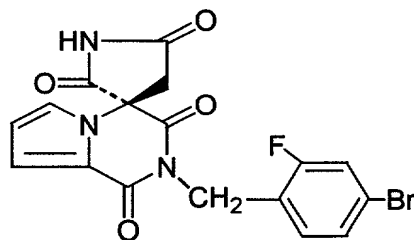
FAST-DISSOLVING PHARMACEUTICAL COMPOSITION

5 TECHNICAL FIELD

The present invention relates to a fast-dissolving pharmaceutical composition of (R)-2-(4-bromo-2-fluorobenzyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-4-spiro-3'-pyrrolidine-1,2',3,5'-tetrone (hereinafter, referred to as "AS-3201") having a potent aldose reductase inhibitory activity.

BACKGROUND ART

AS-3201 is the compound of the following formula. Said compound is described in Example 22 of Japanese Patent No. 2516147 (USP 5258382), Reference Example 12 of JP-A-6-192222 (Chem. Abstr., 122, 9860 (1995)), and Experiment of JP-A-8-176105 (Chem. Abstr., 125, 221569 (1996)), and its potent aldose reductase inhibitory activities are disclosed therein.



25 Example 28 of Japanese Patent No. 2516147 (USP

5258382) describes a method for preparing specific tablets of AS-3201. That is, it is described therein that AS-3201 (1g), corn starch (25 g), lactose (58 g), crystalline cellulose (11 g), hydroxypropylcellulose (3 g), light anhydrous silicic acid (1 g) and magnesium stearate (1 g) are blended, granulated and made into 1,000 tablets each weighing 100 mg by a conventional method.

During the studies on methods for preparing AS-3201-containing pharmaceutical compositions having an excellent bioavailability, the present inventors have found that the water-solubility of said substance is extremely low in the range of low pH to the extent of several $\mu\text{g/ml}$, and therefore, the plasma concentration of AS-3201 varies widely among the individuals to be administered.

Under such circumstances, the present inventors have further intensively studied, and have found that by using micronized AS-3201 in a composition, the dissolution characteristics of said substance from the composition are remarkably improved, and as a result, an AS-3201-containing fast-dissolving pharmaceutical composition having a good bioavailability can be obtained, and finally have accomplished the present invention.

DISCLOSURE OF INVENTION

The present invention provides a fast-dissolving pharmaceutical composition comprising micronized AS-3201.

The terms used in the present specification are explained below.

The "micronized AS-3201" means powders of AS-3201 having a mean particle size of less than about 20 μm . The "mean particle size" means a particle size of being at 50 % in cumulative particle distribution on weight or volume basis (ref., HA Lieberman et al., "Pharmaceutical Dosage Forms: Tablets", Marcel Dekker, Inc., New York, 1990, vol. 2, 174-186; Kouichi IINOYA (edit.) "Handbook of Powder and Particle Measurement (in Japanese)", The NIKKAN KOGYO SHINBUN LTD., 1981, 29-36). The "dissolution test" means a test in which the dissolution of AS-3201 from test pharmaceutical compositions in an amount corresponding to 20 mg of AS-3201 is evaluated according to Paddle method (50 rpm) specified in the Twelfth Edition of the Pharmacopoeia of Japan, using a 0.2 M phosphate buffer (pH 6.5, 900 ml) as a test solution, and assaying AS-3201 by spectrophotometry at 300 nm. The " $\text{pK}_{\text{a}1}$ " means an acid dissociation exponent of an acidic substance at 25°C in an infinitely diluted solution thereof. When an acidic substance is a polybasic acid, it means an acid dissociation exponent at the first step of dissociation. The "water-solubility" means a maximum amount of a solute being dissolved in 100 ml of water. The term "about" is used with the intention of including values following said

term.

The mean particle size of the micronized AS-3201 is preferably less than about 10 μm , more preferably less than about 5 μm , and most preferably in the range of about 0.5 μm to about 3 μm .

According to the method disclosed in Japanese Patent No. 2516147 (USP 5258382), crystals of AS-3201 having a mean particle size of about 60 μm to about 120 μm can usually be obtained. The micronization of AS-3201 crystals is carried out using a mill that is conventionally used in the pharmaceutical field. Mills are, for example, a fluid energy mill such as Jet Mill (manufactured by SEISHIN ENTERPRISE Co., LTD., Japan), a high speed rotative impact mill such as Sample Mill (manufactured by Hosokawa Micron Corporation, Japan), Pin Mill (manufactured by ALPINE, Germany), or Angmill (manufactured by Hosokawa Micron Corporation, Japan), a wet form high speed tumbling trituration mill such as MICROS (manufactured by Nara Machinery Co., Ltd., Japan), and a tumbling mill such as a ball mill. In order to obtain micronized powders having a mean particle size of less than about 5 μm , a fluid energy mill is preferably used. The micronization can be carried out on AS-3201 crystals alone, or on a mixture of AS-3201 crystals and a part or whole of pharmaceutical excipients or carriers, which are used in the preparation of

pharmaceutical compositions.

The AS-3201-containing fast-dissolving pharmaceutical composition of the present invention may be solid dosage forms, and includes, for example, tablets, capsules,

5 granules, powders, etc. These pharmaceutical compositions can be prepared by mixing micronized AS-3201 with

pharmaceutical excipients or carriers such as diluents, disintegrators, binders and lubricants by a conventional

method. For example, the mixture is granulated by wet-

10 granulation such as high-shear granulation, fluid bed granulation, agitation fluid bed granulation, centrifugal fluid bed granulation, or extrusion granulation, or by dry-

granulation such as roller compaction or slugging, and then the resulting granules are put into capsules for capsule

15 preparations, or compressed for tablet preparations.

Alternatively, a mixture of micronized AS-3201 and

pharmaceutical excipients or carriers can directly be put into capsules for capsule preparations, or compressed for

tablet preparations. These pharmaceutical compositions may

20 optionally be coated, or may additionally contain

stabilizers, surfactants, coloring agents, flavoring agents, etc.

The pharmaceutical excipients or carriers may be any ones except for ones showing a bad compatibility with AS-

25 3201. The diluents include, for example, lactose, starch,

crystalline cellulose, D-mannitol, sucrose, glucose, erythritol, xylitol, D-sorbitol, anhydrous dibasic calcium phosphate, and calcium sulfate. The disintegrators are, for example, starch, crystalline cellulose, low substituted hydroxypropylcellulose, carmellose, carmellose calcium, sodium carboxymethyl starch, croscarmellose sodium, partly pregelatinized starch, and hydroxypropyl starch. The binders are, for example, acacia, starch, hydroxypropyl-cellulose, hydroxypropylmethylcellulose, polyvinyl alcohol, pullulan, gelatin, ethylcellulose, methylcellulose, carmellose sodium, and dextrin. The lubricants are, for example, magnesium stearate, calcium stearate, stearic acid, sucrose esters of fatty acids, light anhydrous silicic acid, talc, hydrogenated oil, and macrogol.

The stabilizer may be any pharmaceutically acceptable acidic substances having an acidity more potent than that of AS-3201, i.e., $pK_a = 5.6-5.8$, and preferable acidic substances are ones having a pK_{a1} of less than about 4.5 and a water-solubility of larger than about 10 g/100 ml at 15°C - 25°C. More preferable acidic substances are ones having a pK_{a1} of less than about 3.3 and a water-solubility of larger than about 50 g/100 ml at 15°C - 25°C. Especially preferable acidic substances are, for example, citric acid, tartaric acid, maleic acid, and phosphoric acid. Among these acidic substances, tartaric acid is most

preferable. The content of the acidic substance is preferably in the range of about 0.5 % by weight to about 2.5 % by weight. It is preferable to add a stabilizer in the case of preparing a pharmaceutical composition containing AS-3201 in a ratio of less than about 5 % by weight.

The surfactants to be used in the present pharmaceutical composition are, for example, sorbitan fatty acid esters and polysorbates. The coloring agents are, for example, tar color, caramel, and red iron oxide. The flavoring agents are, for example, sweeteners and perfumes.

The dissolution characteristics of the active substance from the composition can be remarkably improved by using micronized AS-3201, and by further controlling the combination ratio of pharmaceutical excipients or carriers, AS-3201-containing fast-dissolving pharmaceutical compositions having more improved dissolution characteristics as well as good bioavailability can be obtained. The combination ratio of the pharmaceutical excipients or carriers may vary depending on the content of AS-3201. The content of AS-3201 in the present fast-dissolving pharmaceutical composition is usually in the range of about 0.5 % by weight to about 25 % by weight, to the total weight of the pharmaceutical composition. When the content of AS-3201 is in the range of about 0.5 % by

weight to 5 % by weight to the total weight of the pharmaceutical composition, then the pharmaceutical composition usually comprises a diluent in a ratio of about 51 % by weight - about 93.8 % by weight, a disintegrator in a ratio of about 5 % by weight - about 35 % by weight, a binder in a ratio of about 0.5 % by weight - about 5 % by weight, and a lubricant in a ratio of about 0.2 % by weight - about 4 % by weight. More preferably, the pharmaceutical composition comprises a diluent in a ratio of about 59 % by weight - about 88 % by weight, a disintegrator in a ratio of about 10 % by weight - about 30 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight - about 3 % by weight. When the content of AS-3201 is more than 5 % by weight and less than about 25% by weight to the total weight of the pharmaceutical composition, then the present composition usually comprises a diluent in a ratio of about 16 % by weight - about 84.3 % by weight, a disintegrator in a ratio of about 10 % by weight - about 50 % by weight, a binder in a ratio of about 0.5 % by weight - about 5 % by weight, and a lubricant in a ratio of about 0.2 % by weight - about 4 % by weight, and more preferably, a diluent in a ratio of about 29 % by weight - about 73.5 % by weight, a disintegrator in a ratio of about 20 % by weight - about 40 % by weight, a binder in a ratio of about 1 % by weight

- about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight - about 3 % by weight.

Since AS-3201 has an extremely low water-solubility to the extent of several $\mu\text{g/ml}$ in the range of low pH, there is a correlation between the initial dissolution rate and the bioavailability of AS-3201-containing pharmaceutical compositions, and compositions having a better initial dissolution rate can show a better bioavailability. From the viewpoint of the above, preferable compositions are ones having a dissolution percentage of the active substance of 50 % or more for 15 minutes after the start of the dissolution test, and more preferable pharmaceutical compositions are ones having a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

The AS-3201-containing fast-dissolving pharmaceutical composition of the present invention may be packed in a bottle using materials of low moisture-permeability or in damp-proof packages such as heat-sealed packages, if necessary.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 is a graph showing a dissolution pattern of the tablets of Examples 1 and 2, and Comparative Example 1.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated in more detail by

Examples and Comparative Example, but the present invention should not be construed to be limited thereto. The mean particle size was measured using a laser diffraction particle size distribution analyzer (HELOS & RODOS (trademark), manufactured by SYMPATEC GmbH, Germany), and calculated from cumulative particle distribution on volume basis by dry air dispersion method (dispersion air pressure: 0.5 atm).

Example 1

10 Preparation of tablets:

	AS-3201	160 g
	Tartaric acid	8 g
	Lactose	492 g
	Low substituted hydroxypropylcellulose	300 g
15	Hydroxypropylcellulose	20 g
	<u>Magnesium stearate</u>	<u>20 g</u>
	Total	1000 g

AS-3201 crystals were micronized using Single Truck Jet Mill (manufactured by SEISHIN ENTERPRISE CO., LTD., hereinafter abbreviated as "Jet Mill") with compression air pressure of 6 kgf/cm² to give powders having a mean particle size of about 1.5 μ m. The micronized AS-3201 powders thus obtained, lactose, and low substituted hydroxypropylcellulose were charged into a fluid bed granulator and drier, and then the mixture was granulated

by spraying thereto a solution of tartaric acid in a 5 % aqueous hydroxypropylcellulose solution. The granules were dried, and thereto was added magnesium stearate, and the mixture was blended in a V-blender. The resultant was compressed on a rotary tableting machine to give tablets weighing 125 mg and containing 20 mg of AS-3201 each.

Example 2

Preparation of tablets:

AS-3201 crystals were micronized by Sample Mill (manufactured by Hosokawa Micron Corporation) to give powders having a mean particle size of about 10 μ m. The micronized AS-3201 powders thus obtained were granulated, dried and compressed in the same manner as in Example 1, to give tablets weighing 125 mg and containing 20 mg of AS-3201 each.

Comparative Example 1

Preparation of tablets:

Non-micronized AS-3201 crystals having a mean particle size of about 87 μ m were granulated, dried and compressed in the same manner as in Example 1, to give tablets weighing 125 mg and containing 20 mg of AS-3201 each.

Experiment 1

Dissolution test:

The dissolution of the active substance from the tablets obtained in Examples 1 and 2 and Comparative

Example 1 was evaluated according to Paddle method (50 rpm) specified in the Twelfth Edition of the Pharmacopoeia of Japan, using a 0.2 M phosphate buffer (pH 6.5, 900 ml) as a test solution. The quantitative assay of AS-3201 was carried out by spectrophotometry at 300 nm.

The results are shown in Fig. 1. Each point of Fig. 1 shows the mean value of the results in three repeats of the experiments on each tablet of Example 1, Example 2 and Comparative Example 1.

As is shown in Fig. 1, the tablets of Example 1 and Example 2 show remarkably improved dissolution characteristics, as compared with the tablets of Comparative Example 1.

Example 3

Preparation of tablets:

AS-3201	160 g
Tartaric acid	10 g
Lactose	600 g
Low substituted hydroxypropylcellulose	200 g
Hydroxypropylcellulose	20 g
<u>Magnesium stearate</u>	<u>10 g</u>
Total	1000 g

The above components were treated in the same manner as in Example 1, and compressed to give tablets weighing 125 mg and containing 20 mg of AS-3201 each. The

dissolution percentage of the active substance from the tablets thus obtained for 15 minutes after the start of the dissolution test was 72.6 %.

Example 4

5 Preparation of tablets:

	AS-3201	20 g
	Tartaric acid	8 g
	Lactose	732 g
	Low substituted hydroxypropylcellulose	200 g
10	Hydroxypropylcellulose	20 g
	<u>Magnesium stearate</u>	<u>20 g</u>
	Total	1000 g

AS-3201 crystals were micronized using Jet Mill with compression air pressure of 6 kgf/cm², and the resultant was charged into a fluid bed granulator and drier together with lactose and low substituted hydroxypropylcellulose, and then, the resultant was granulated by spraying thereto a solution of tartaric acid in a 5 % aqueous hydroxypropylcellulose solution. The granules were dried, and thereto was added magnesium stearate, and the mixture was blended in a V-blender. The resultant was compressed on a rotary tableting machine to give tablets weighing 125 mg and containing 2.5 mg of AS-3201 each.

The dissolution percentage of the active substance from the tablets thus obtained for 15 minutes after the

start of the dissolution test was 93.0 %.

Example 5

Preparation of tablets:

	AS-3201	80 g
5	Tartaric acid	4 g
	Lactose	246 g
	Low substituted hydroxypropylcellulose	150 g
	Hydroxypropylcellulose	10 g
	<u>Magnesium stearate</u>	<u>10 g</u>
10	Total	500 g

AS-3201 crystals were micronized using Jet Mill with compression air pressure of 6 kgf/cm², and thereto were added lactose and low substituted hydroxypropylcellulose, and then, the resulting mixture was blended in a Versatile Mixer for 5 minutes. To the mixture was added a solution of tartaric acid in a 4 % aqueous hydroxypropylcellulose solution, and the mixture was further kneaded for 10 minutes. The mixture was dried, and thereto was added magnesium stearate, and the resulting mixture was compressed on a single-punch tableting machine to give tablets weighing 125 mg and containing 20 mg of AS-3201 each.

The dissolution percentage of the active substance from the tablets thus obtained for 15 minutes after the start of the dissolution test was 93.2 %.

Example 6

Preparation of tablets:

	AS-3201	144 g
	Lactose	549 g
5	Low substituted hydroxypropylcellulose	180 g
	Hydroxypropylcellulose	18 g
	<u>Magnesium stearate</u>	<u>9 g</u>
	Total	900 g

AS-3201 crystals were micronized using Jet Mill with
 10 compression air pressure of 6 kgf/cm², and the resultant
 was put into a fluid bed granulator and drier together with
 lactose and low substituted hydroxypropylcellulose, and
 then, the mixture was granulated by spraying thereto a 5 %
 aqueous hydroxypropylcellulose solution. After drying, to
 15 the granules was added magnesium stearate, and the mixture
 was blended in a V-blender. The resultant was compressed
 on a rotary tableting machine to give tablets weighing 125
 mg and containing 20 mg of AS-3201 each.

The dissolution percentage of the active substance
 20 from the tablets thus obtained for 15 minutes after the
 start of the dissolution test was 92.0 %.

Examples 7-9

Preparation of tablets:

	<u>Ex. 7</u>	<u>Ex. 8</u>	<u>Ex. 9</u>
25	AS-3201	40 g	40 g

	Tartaric acid	8 g	8 g	8 g
	Lactose	712 g	672 g	632 g
	Low substituted hydroxy- propylcellulose	200 g	240 g	280 g
5	Hydroxypropylcellulose	20 g	20 g	20 g
	<u>Magnesium stearate</u>	<u>20 g</u>	<u>20 g</u>	<u>20 g</u>
	Total	1000 g	1000 g	1000 g

AS-3201 micronized using Jet Mill was granulated,
dried and compressed in the same manner as in Example 1 to
10 give tablets weighing 125 mg and containing 5 mg of AS-3201
each.

The dissolution percentages of the active substance
from the tablets of Examples 7, 8 and 9 for 15 minutes
after the start of the dissolution test were 91.0 %, 94.5 %
15 and 92.7 %, respectively.

Examples 10-12

Preparation of tablets:

		<u>Ex. 10</u>	<u>Ex. 11</u>	<u>Ex. 12</u>
	AS-3201	80 g	80 g	80 g
20	Tartaric acid	8 g	8 g	8 g
	Lactose	672 g	632 g	592 g
	Low substituted hydroxy- propylcellulose	200 g	240 g	280 g
	Hydroxypropylcellulose	20 g	20 g	20 g
25	<u>Magnesium stearate</u>	<u>20 g</u>	<u>20 g</u>	<u>20 g</u>
	Total	1000 g	1000 g	1000 g

AS-3201 micronized using Jet Mill was granulated, dried and compressed in the same manner as in Example 1 to give tablets weighing 125 mg and containing 10 mg of AS-3201 each.

5 The dissolution percentages of the active substance from the tablets of Examples 10, 11 and 12 for 15 minutes after the start of the dissolution test were 89.4 %, 91.6 % and 92.2 %, respectively.

INDUSTRIAL APPLICABILITY

10 As explained above, the AS-3201-containing fast-dissolving pharmaceutical composition of the present invention has improved dissolution characteristics as well as a good bioavailability.

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CLAIMS

1. A fast-dissolving pharmaceutical composition comprising micronized (R)-2-(4-bromo-2-fluorobenzyl)-
5 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-4-spiro-3'-pyrrolidine-1,2',3,5'-tetrone (hereinafter, referred to as "AS-3201").

2. The fast-dissolving pharmaceutical composition according to claim 1, wherein the mean particle size of the
10 micronized AS-3201 is less than about 10 μm .

3. The fast-dissolving pharmaceutical composition according to claim 1, wherein the mean particle size of the micronized AS-3201 is less than about 5 μm .

4. The fast-dissolving pharmaceutical composition
15 according to claim 1, wherein the mean particle size of the micronized AS-3201 is in the range of about 0.5 μm - about 3 μm .

5. The fast-dissolving pharmaceutical composition according to any one of claims 1-4, which comprises the
20 micronized AS-3201 in a ratio of about 0.5 % by weight - 5 % by weight, a diluent in a ratio of about 51 % by weight - about 93.8 % by weight, a disintegrator in a ratio of about 5 % by weight - about 35 % by weight, a binder in a ratio of about 0.5 % by weight - about 5 % by weight, and a
25 lubricant in a ratio of about 0.2 % by weight - about 4 %

by weight, to the total weight of the pharmaceutical composition.

6. The fast-dissolving pharmaceutical composition according to claim 5, which comprises a diluent in a ratio of about 59 % by weight - about 88 % by weight, a disintegrator in a ratio of about 10 % by weight - about 30 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about 0.5 % by weight - about 3 % by weight.

7. The fast-dissolving pharmaceutical composition according to any one of claims 1-4, which comprises the micronized AS-3201 in a ratio of more than 5 % by weight and less than about 25% by weight, a diluent in a ratio of about 16 % by weight - about 84.3 % by weight, a disintegrator in a ratio of about 10 % by weight - about 50 % by weight, a binder in a ratio of about 0.5 % by weight - about 5 % by weight, and a lubricant in a ratio of about 0.2 % by weight - about 4 % by weight, to the total weight of the pharmaceutical composition.

8. The fast-dissolving pharmaceutical composition according to claim 7, which comprises a diluent in a ratio of about 29 % by weight - about 73.5 % by weight, a disintegrator in a ratio of about 20 % by weight - about 40 % by weight, a binder in a ratio of about 1 % by weight - about 3 % by weight, and a lubricant in a ratio of about

0.5 % by weight - about 3 % by weight.

9. The fast-dissolving pharmaceutical composition according to any one of claims 1-8, which has a dissolution percentage of the active substance 50 % or more for 15 minutes after the start of the dissolution test.

10. The fast-dissolving pharmaceutical composition according to claim 9, which has a dissolution percentage of the active substance of 80 % or more for 15 minutes after the start of the dissolution test.

11. The fast-dissolving pharmaceutical composition according to any one of claims 1-10, which contains as a stabilizer at least one acidic substance having an acidity more potent than that of AS-3201.

12. The fast-dissolving pharmaceutical composition according to claim 11, wherein the acidic substance is a member selected from the group consisting of citric acid, tartaric acid, maleic acid and phosphoric acid.

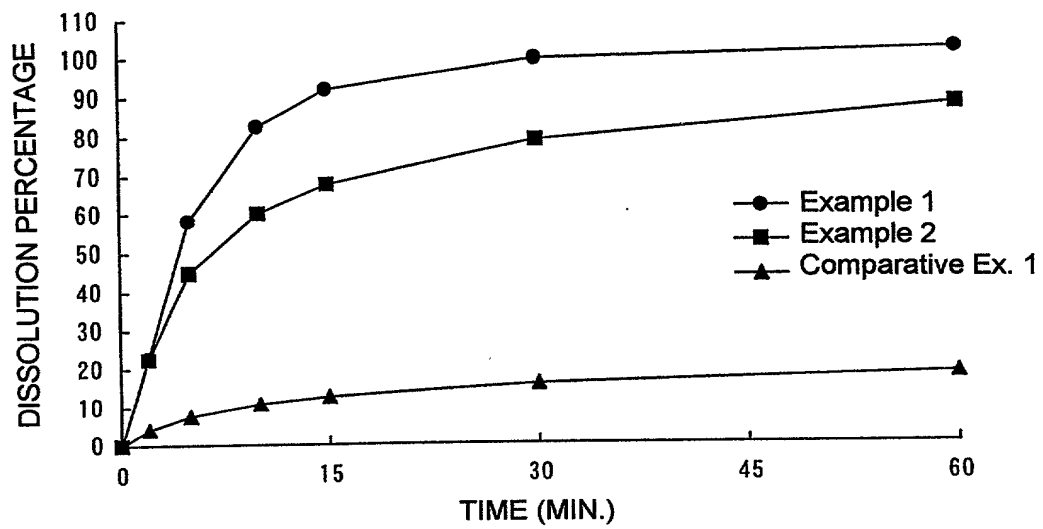
ABSTRACT

A fast-dissolving pharmaceutical composition comprising micronized (R)-2-(4-bromo-2-fluorobenzyl)-
5 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-4-spiro-3'-pyrrolidine-1,2',3,5'-tetrone (hereinafter, referred to as AS-3201). The present pharmaceutical composition has improved dissolution characteristics as well as a good bioavailability.

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FIG. 1



DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION

(X) Original () Supplemental () Substitute () PCT () Design

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Title: FAST-DISSOLVING PHARMACEUTICAL COMPOSITION

of which is described and claimed in:

() the attached specification, or

() the specification in the application Serial No. _____ filed _____;

and with amendments through _____ (if applicable), or

(X) the specification in International Application No. PCT/ JP98/04658, filed Oct. 15, 1998, and as amended on _____ (if applicable).

I hereby state that I have reviewed and understand the content of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge my duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 (and §172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NO.	DATE OF FILING	PRIORITY CLAIMED
Japan	306635/1997	October 20, 1997	Yes

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

APPLICATION SERIAL NO.	U.S. FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

7

And I hereby appoint John T. Miller, Reg. No. 21,120; Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Jeffrey Nolton, Reg. No. 25,408; Warren M. Cheek, Jr., Reg. No. 33,367; Nils E. Pedersen, Reg. No. 33,145 and Charles R. Watts, Reg. No. 33,142, who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., attorneys to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

I hereby authorize the U.S. attorneys named herein to accept and follow instructions from AOYAMA & PARTNERS as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.

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I further declare that all statements made herein of my own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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 7th Inventor _____ Date _____

The above application may be more particularly identified as follows:

U.S. Application Serial No. _____ Filing Date _____
 Applicant Reference Number _____ Atty Docket No. _____
 Title of Invention _____
